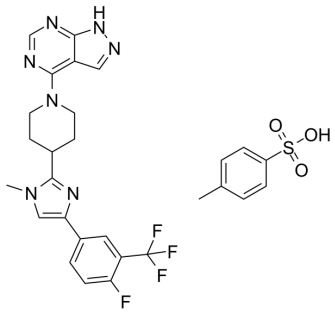
LY-2584702 tosylate salt

Cat. No.:	HY-12493A
CAS No.:	1082949-68-5
Molecular Formula:	$C_{28}H_{27}F_4N_7O_3S$
Molecular Weight:	617.62
Target:	Ribosomal S6 Kinase (RSK)
Pathway:	MAPK/ERK Pathway
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 1 years; -20°C, 6 months (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 10.25 mg/mL (16.60 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6191 mL	8.0956 mL	16.1912 mL
	5 mM	0.3238 mL	1.6191 mL	3.2382 mL
	10 mM	0.1619 mL	0.8096 mL	1.6191 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1 mg/mL (1.62 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 1 mg/mL (1.62 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1 mg/mL (1.62 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LY-2584702 tosylate salt is a selective ATP competitive inhibitor of p70S6K with an IC_{50} of 4 nM. In S6K1 enzyme assay, the IC_{50} of LY-2584702 is 2 nM.

IC_{50} & Target

p70S6K
4 nM (IC_{50})

In Vitro

LY-2584702 (LY2584702) inhibits phosphorylation of the S6 ribosomal protein (pS6) in HCT116 colon cancer cells with an IC_{50} of 0.1-0.24 μM[1]. In S6K1 enzyme assay, the IC_{50} of LY-2584702 (LY2584702) is 2 nM. For pS6 inhibition in cells, the IC_{50}=100 nM. LY-2584702 has some activity against the S6K-related kinases MSK2 and RSK at high concentrations (enzyme assay IC_{50}

	=58-176 nM). LY-2584702 inhibits S6K activity in EOMA cells, as determined by the phosphorylation of its downstream effector S6, in a dose-dependent manner[2]. Proliferation of A549 is significantly inhibited by LY-2584702 (LY2584702) treating over 24 h at 0.1 μM ($P<0.05$); and the trend of decline is more conspicuous with longer treatment and/or with the increased drug concentration (all $P<0.05$). Similar results are also observed in SK-MES-1, although the obvious inhibition is led by LY-2584702 at 0.6 μM ($P<0.05$), much higher than that of A549[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	LY-2584702 demonstrates significant single-agent efficacy in both U87MG glioblastoma and HCT116 colon carcinoma xenograft models at two dose levels of 2.5 mg/kg twice daily (BID) and 12.5 mg/kg BID. LY-2584702 demonstrates statistically significant tumour growth reduction at TMED50 (threshold minimum effective dose 50%) (2.3 mg/kg) and TMED90 (10 mg/kg) in the HCT116 colon carcinoma xenograft model[1]. To examine the role of S6K in vivo, EOMA cells expressing shAkt3 are implanted in nu/nu mice, then treated for 14 days with LY-2584702 or Rapamycin. Analysis of tumors removed after 14 days shows that LY-2584702 inhibits S6 phosphorylation almost as effectively as Rapamycin. Loss of Akt3 increases tumor growth as compared with pLKO. LY-2584702 treatment alone does not significantly affect the growth of pLKO tumors. However, LY-2584702 significantly reduces the growth of tumors with shAkt3[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	LY-2584702 is fully dissolved in 20 mL 10% DMSO and reserved at -80°C. When conducted the experiments in vitro, LY-2584702 is further diluted in 0.5% Tween 80, 5% propylene glycol and 30% PEG400 to reach different DMSO concentrations of 0.1 μM, 0.2 μM, 0.6 μM, and 1.0 μM. Cell Counting Kit-8 (CCK-8) is used to measure the cells proliferation in vitro. Cell lines A549 and SK-MES-1 treated by LY-2584702 for 24 h with different concentrations are seeded in 96-well plates at a density of 5×10^3 per well, with six repeats. DMSO treated, or in other words, the concentration of LY-2584702 of 0 is used as negative control. Cells absorbance at 450 nm is detected every 24 h after seeding to measure the proliferative activities[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] LY-2584702 is prepared in 0.25% Tween-80 and 0.05% antifoam, and administered orally to mice (12.5 mg/kg twice daily). EOMA cells (0.3×10^6) are injected subcutaneously in 6- to 8-week-old nu/nu female mice (2 sites/mouse, 4-5 mice/group). Tumor size is measured daily. For drug treatment, when tumors reach 0.01 cm^3 in size, the animals are treated with vehicle control or LY-2584702 (12.5 mg/kg twice daily, oral dosing). Tumor size is measured every 3 to 4 days[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Immunity. 2021 Sep 14;54(9):2042-2056.e8.
- Hepatology. 2022 Sep 21.
- Theranostics. 2022 Jan 1;12(3):1204-1219.
- Pharmacol Res. 2021 Oct 4;105871.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Tolcher A, et al. A phase I trial of LY2584702 tosylate, a p70 S6 kinase inhibitor, in patients with advanced solid tumors. Eur J Cancer. 2014 Mar;50(5):867-75.

[2]. Phung TL, et al. Akt1 and akt3 exert opposing roles in the regulation of vascular tumor growth. Cancer Res. 2015 Jan 1;75(1):40-50.

[3]. Chen B, et al. Hyperphosphorylation of RPS6KB1, rather than overexpression, predicts worse prognosis in non-small cell lung cancer patients. PLoS One. 2017 Aug 9;12(8):e0182891.

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